

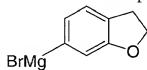
The process as recited above, wherein the first or second aprotic solvent is selected from the group consisting of tetrahydrofuran, acetonitrile, dimethylacetamide, dimethylformamide, diethyl ether,

N-methylpyrrolidinone, dichloromethane, methyl t-butyl ether, toluene, benzene, hexane, pentane, dioxane, and a mixture thereof. A preferred first aprotic solvent is a 1:1 mixture of N-methylpyrrolidinone and tetrahydrofuran at temperature range of about -40°C to about -50°C or N-methylpyrrolidinone at temperature range of about -20°C to about -10°C . A preferred second aprotic solvent is THF or a mixture of THF/toluene.


The process as recited above, wherein the additive is selected from the group consisting of $\text{MgBr}_2 \cdot \text{Et}_2\text{O}$, LiBr , $\text{BF}_3 \cdot \text{ET}_2\text{O}$, ArLi , and DMPU.

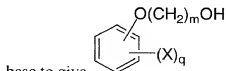
The process as recited above, wherein the Grignard reagent is ArMgX , which is prepared from ArX and Mg .


The process as recited above, wherein the Grignard reagent is



The process as recited above, wherein ArX is prepared by the following steps:

(a) reacting  with $\text{HO}(\text{CH}_2)_m\text{OH}$ in the presence of a



base to give , wherein q is 1 to 5, m is 2, 3, or 4 and X is Br , Cl , F , or I ;

(b) halogenating $-\text{O}(\text{CH}_2)_m\text{OH}$ substituent of the benzene to produce the benzene with $-\text{O}(\text{CH}_2)_m\text{X}$ substituent in the presence of an aprotic solvent, water, and halogenating agent at a temperature range of about 0°C to about 90°C ; and

(c) cyclizing the compound produced in step (b) in the presence of alkyl lithium or aryl lithium to give ArX .

The process as recited above, wherein the ArX is 6-bromo-2,3-dihydrobenzofuran.

The process as recited above, wherein the temperature range in Grignard addition reaction is about -40°C to about -50°C .

- The process as recited above, wherein the phosphoramidate reagent is N,N,N,N-tetra($\text{C}_1\text{-C}_6$)-alkylphosphorodiamidic halide or N,N,N,N-tetraarylphosphorodiamidic halide, preferably
- 5 N,N,N,N-tetramethylphosphorodiamidic chloride, $[(\text{CH}_3)_2\text{N}]_2\text{POCl}$ or N,N,N,N-tetramethylphosphorodiamidic bromide, $[(\text{CH}_3)_2\text{N}]_2\text{POBr}$, N,N,N,N-tetraethylphosphorodiamidic chloride, $[(\text{CH}_3\text{CH}_2)_2\text{N}]_2\text{POCl}$ or N,N,N,N-tetraethylphosphorodiamidic bromide, $[(\text{CH}_3\text{CH}_2)_2\text{N}]_2\text{POBr}$
- 10 N,N,N,N-tetraisopropylphosphorodiamidic chloride $[(\text{CH}_3)_2\text{CH}]_2\text{N}]_2\text{POCl}$ or N,N,N,N-tetraisopropylphosphorodiamidic bromide, $[(\text{CH}_3)_2\text{CH}]_2\text{N}]_2\text{POBr}$, N,N,N,N-tetraphenylphosphorodiamidic chloride, or N,N,N,N-tetraphenylphosphorodiamidic bromide.

- The process as recited above wherein the base is selected from the
- 15 group consisting of n-butyl lithium, phenyl lithium, potassium *tert*-butoxide, sodium hydride, lithium diisopropylamide, lithium diethylamide, lithium dimethylamide, potassium hexamethyldisilazide, sodium hexamethyldisilazide, and lithium hexamethyldisilazide. The preferred base is sodium hexamethyldisilazide, which is present in amounts between about 1 equivalent and about 6 equivalents relative to the
- 20 amount of the phosphoramidate reagent or N,N,N',N'-tetramethylphosphorodiamidic chloride.

The process as recited above, wherein the temperature range for the cyclization in the presence of phosphoramidate reagent is about -20°C to about 25°C .

- 25 The process as recited above, which further comprises the steps of:
- (a) deprotecting the cyclized compound of Formula IV by removing protecting groups with acid at a temperature range of about 0°C to about 25°C ;
- (b) crystallizing the deprotected compound as benzylamine salt; and
- (c) hydrogenating the deprotected compound in the presence of a
- 30 hydrogenation catalyst and a protic solvent at a temperature range of about 25°C to about 40°C .

The process as recited above, wherein the hydrogenation catalyst is Pd/C.

The process as recited above, wherein the protic solvent is selected from the group consisting of (C₁-C₆)-alcohol, H₂O, and a mixture thereof. The preferred protic solvent is methanol.

- 5 It is further understood that the substituents recited above would include the definitions recited below.

As used herein, the term "alkyl," unless otherwise indicated, includes those alkyl groups of a designated number of carbon atoms of either a straight, branched, or cyclic configuration. Examples of "alkyl" include methyl, ethyl, propyl, isopropyl, butyl, *sec*-butyl, *tert*-butyl, pentyl, hexyl, heptyl, neopentyl, isopentyl, and the like.

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Cycloalkyl denotes rings composed of 3 to 8 methylene groups, each of which may be optionally substituted with other hydrocarbon substituents. Examples of cycloalkyls include, but are not limited to: cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, 4-methylcyclohexyl, cycloheptyl, and the like.

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The term "alkenyl" includes hydrocarbon chains of a specified number of carbon atoms of either a straight or branched configuration and at least one unsaturation, which may occur at any point along the chain, such as ethenyl, propenyl, butenyl, pentenyl, vinyl, allyl, 2-butenyl and the like.

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The term "alkoxy" represents an alkyl group of indicated number of carbon atoms attached through an oxygen bridge, such as methoxy, ethoxy, propoxy, isopropoxy, butoxy, *tert*-butoxy, pentoxy, and the like.

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The term "aryl," unless specifically defined otherwise, is defined as phenyl and 1-naphthyl or 2-naphthyl, including aryl substituted with a 5- or 6-membered fused ring, such as an unsubstituted and substituted 2,3-dihydrobenzofuran, methylenedioxy, oxazolyl, imidazolyl, or thiazolyl ring. Aryl as defined above may be optionally substituted with one to three of the substituents as set forth in the embodiments recited above.

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The heteroaryl substituents represent but are not limited to: a carbazolyl, furanyl, thienyl, pyrrolyl, isothiazolyl, imidazolyl, isoxazolyl, thiazolyl, oxazolyl, pyrazolyl, pyrazinyl, pyridyl, pyrimidyl, and purinyl.

The heterocycl substituents represent but are not limited to: oxazolidinyl, thiazolidinyl, imidazolidinyl, thiazolidinyl, oxadiazolyl, thiadiazolyl, morpholinyl, piperidinyl, piperazinyl, and pyrrolidinyl.